

Inflammatory Mediators in Smoke Inhalation Injury[§]

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Abstract: Smoke inhalation occurs in 10% to 30% of patients admitted to burn centers, and increases mortality by a maximum of 20% over that predicted by age and extent of cutaneous burn alone. Pneumonia in these patients then further increases mortality by a maximum of 40%. While one estimate suggested that 75% of deaths following burn injury may be accounted for by inhalation injury, more recent cohort studies have suggested there is a decreasing mortality attributable to inhalation injury. As part of understanding and improving outcomes from burn injuries, the pathophysiology and inflammatory processes involved in smoke inhalation injury has been extensively investigated in animal models. This review will emphasize the inflammatory pathways involved in inhalation injury, and targeted methods used to treat this injury in both experimental and human models.

Keywords: Smoke inhalation injury, burns, inhalation, inflammation, animal models.

INTRODUCTION

Smoke inhalation injury occurs in 10-30% of thermally injured patients admitted to burn centers in the United States [1]. Despite effective fluid resuscitation management and early surgical excision of burned tissue, mortality rates for combined burn and smoke inhalation injury remain high. The addition of inhalation injury independently increases the risk of death in burn patients by 20% [2, 3]. The secondary development of pneumonia, which in many cases may be the direct result of inhalation injury, further independently increases mortality by a maximum of 40% at the midrange of age and burn size [4]. One estimate suggests that 75% of deaths from burn injury may be accounted for by the inhalation injury component. More recent cohort studies have suggested there is a decreasing mortality from inhalation injury, in concert with the overall improvement in the care of patients with cutaneous burns [5]. Changes in ventilator management likely contributed significantly to this reduction in mortality [6].

In order to improve outcomes with smoke inhalation injury, extensive research has been performed primarily in experimental animal models and to a lesser degree in burn patients. These studies have helped to identify the complex pathophysiologic and inflammatory mechanisms involved in smoke inhalation injury, and have provided experimental models for evaluation of various treatments aimed at controlling these mechanisms. Despite the extensive research done on smoke inhalation in animal models, there is relatively

little research involving novel therapies for inhalation injury performed in humans. The intent of this review is to delineate inflammatory mediators and pathways involved in smoke inhalation injury and provide a basis for future research and novel therapies to improve outcome.

PATHOPHYSIOLOGY OF INHALATION INJURY

Anatomically, smoke inhalation injury may be classified as producing 1) injury to the upper airways including the glottis; 2) injury to the lower airways and lung parenchyma; and 3) systemic toxicity due to inhalation of toxic gases such as cyanide and carbon monoxide [7].

Lung injury from smoke inhalation is associated with tracheobronchial hyperemic sloughing of ciliated epithelium, formation of copious tracheal exudates, and pulmonary capillary permeability changes that result in pulmonary edema. Most importantly, these changes are primarily found in the small airways and lead to the subsequent development of obstruction, hypoxemia, alveolar collapse and finally pneumonia [7]. Other studies show a progressive increase in alveolar-capillary-membrane permeability soon after injury. The inhalation of toxic smoke causes the release of thromboxane and other mediators, which increase pulmonary artery pressure and causes secondary damage to the respiratory epithelium, along with release of chemotactic factors. Neutrophils subsequently undergo diapedesis from the pulmonary microvasculature and release enzymes such as elastase and free oxygen radicals, disrupting endothelial junctions and the epithelial integrity, thus permitting an exudate of protein-rich plasma to enter the lung [8, 9]. A concomitant reduction in the pulmonary immune function and disruption in airway integrity leads to bacterial growth and clinical pneumonia.

The lung has two separate blood supplies (the pulmonary circulation and systemic bronchial circulation), each of which can contribute to lung edema. Under normal conditions, the pulmonary blood supply is equivalent to the car-

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diac output, whereas the bronchial blood flow is roughly 1% of the cardiac output. After smoke inhalation injury, there is a marked increase in bronchial blood flow, which results in pulmonary edema. In an ovine smoke inhalation model, airway blood flow increases eightfold or more in the mainstem bronchi after injury, whereas cardiac output and peripheral tissue blood flow remains relatively unchanged [10]. Bronchial blood flow enters into the pulmonary vasculature through various bronchopulmonary anastomoses. It has been suggested that the bronchial circulation plays a significant role in the spread of inflammatory mediators (and thus the injury process) from the airway to the parenchyma. This increased bronchial blood flow, and thus increased spread of inflammatory mediators, disrupts endothelial junctions and epithelial integrity, leading to the formation of pulmonary edema. Additionally, there may be significant alterations in pulmonary blood flow due to hypoxic pulmonary vasoconstriction, in an effort to match lung perfusion to ventilation and thus to defend pulmonary gas exchange [11].

Widespread plugging of airways by casts and plugs is a severe problem in smoke inhalation injury. In ovine models, necrosis and sloughing of respiratory tract epithelium begins 15 minutes after exposure and may result in full thickness ulceration with higher smoke doses. Mucous production increases by 12 hours and the acute inflammatory process peaks at 24 hours. There is formation of extensive pseudomembranes that ultimately may occlude the major airways. In many cases, the cast are solid and difficult to remove. In addition, ciliary transport function is damaged by smoke inhalation, contributing to ineffective clearance of secretions and thus to airway obstruction [12]. Pathological studies have shown that the obstructing material is mainly composed of infiltrated neutrophils, bronchial epithelial cells, mucus, and fibrin. Obstruction of the terminal airways leads to atelectasis and ultimately bacterial colonization at 72 hours post injury [12, 13].

When neutrophils are activated in inhalation injury as a consequence of cytokine stimulation or ischemia, they primarily accumulate in the lung. There are several possible reasons for this: 1) the pulmonary vascular bed is extensive; 2) pulmonary capillaries are narrower than systemic capillaries; 3) neutrophils lose their deformability when they are activated, and stiffened neutrophils tend to be trapped in the capillaries; 4) pulmonary capillary pressure is lower than that of the systemic circulation; and 5) there is more cytokine production in the lung because of alveolar macrophages [14]. Activated neutrophils adhere to the activated endothelial cells and injure them, resulting in an increase in pulmonary vascular permeability. The exuded plasma contains coagulation factors such as fibrinogen and prothrombin. In addition to the exudation, pulmonary epithelial cells and alveolar macrophages express tissue factor. Tissue factor is an initiator of the extrinsic pathway of coagulation and is known to cause fibrin deposition in the alveolar space. Fibrin formation in the alveolar space is considered to be a hallmark of acute and chronic lung injury [14], and studies of the role of intraalveolar coagulation are ongoing in our laboratory.

ANIMAL MODELS OF INJURY

Large animal models, unlike rodents or other small animals, permit examination of clinically relevant variables and

employ technology such as mechanical ventilators that replicate the care provided in a human intensive care unit. The early animal model for smoke inhalation injury was the goat [15], which was then readily adapted to sheep. Most subsequent large animal studies have been performed in sheep, and to a lesser extent in swine. In these models, injury is induced by delivery of cooled smoke from burning cotton or wood bark chips.

Physiologic variables in the model described by Shimazu responded to the "dose" of smoke (measured as the number of breaths delivered), although not always in a linear manner. Thus, compensatory mechanisms appear to defend against a decrease in the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PFR) until a certain "threshold" smoke dose has been delivered; thereafter, decreases in PFR are steep [11, 16]. Pathologically, these models demonstrate evidence of tracheal and lobar bronchial mucosal sloughing with pseudomembrane formation, in addition to areas of congestion and edema found adjacent to the peribronchial tree. They likewise demonstrate diffuse pulmonary mucosal sloughing, pulmonary edema, and decrease in systemic oxygen tension. Importantly, airway findings in both goat and sheep models paralleled bronchoscopic evidence of airway changes seen in humans. These models have focused primarily on inflammatory changes due to alterations of blood flow in the lungs, the effect of smoke on the airways, alterations in cellular immune responses, and evaluation of other possible mediators of injury.

Blood and Lymph Flow

Early studies evaluated blood and lung lymph flow to ascertain whether these changes were responsible for airway and parenchymal changes. Measurement of lung lymph flow and lymph/plasma protein ratio demonstrated an increase in overall microvascular permeability resulting in pulmonary edema that was directly related to the duration of exposure [17, 18]. Further studies indicated that bronchial blood flow peaked at 20 minutes after smoke exposure and remained increased at 6-8 times normal flow for 24 hours. Lung lymph flow also increased 600% during this time period but no correlation existed between bronchial and lymph flows [19]. It was further demonstrated that 24 hours after inhalation injury, increased capillary permeability accounts for 66% of lung injury while at 48 hours, there is a shift to increased capillary pressure that is responsible for 75% of measured lung injury [20].

Effect on Cell Populations

Further work then centered on cell populations within the lungs that are responsible for the pathophysiologic changes to the airway and parenchyma. Primary morphologic changes were noted to cause acute cell-membrane damage in trachea and bronchi leading to edema, progressive necrotizing tracheobronchitis with pseudomembrane formation and airway obstruction. The loss of ciliated cells also indicated the first morphologic injury to tracheal epithelium (regardless of smoke dose and large amount of mucous on surface of epithelium) [10]. There were found to be changes in type I and type II cells without evidence of capillary endothelial changes [12] and further evidence suggested the type of smoke (wood versus cotton) could inhibit surfactant activity in type II epithelial cells harvested from dog lungs [21].

Treatment with exogenous surfactant after smoke inhalation injury in a single study improved PaO₂, static lung compliance, and dynamic surface tension [22].

Oxidative Stress

Much of the research on smoke inhalation injury has focused on the causative role of oxidative stress in leading to lung injury. Early animal models noted an increase in pulmonary extravascular neutrophil concentrations and likewise a consumptive depletion of antiproteases as a surrogate measure for enzyme activity [8]. Further study of antiprotease depletion in leukocyte-depleted sheep did not result in elevated production of oxygen-derived free radicals or consumption of antiproteases, thus suggesting the neutrophil as one inflammatory mediator responsible for the production of free radicals [23]. Similar findings were found in alveolar macrophage populations in which decreased bacterial phagocytosis and killing in addition to decreased phagocytosis of apoptotic neutrophils [24]. Further work indicated that in addition to decreased function of alveolar macrophages, harvesting of alveolar macrophages within 70 minutes of injury showed increased superoxide production, primary tumor necrosis factor- α (TNF- α) release and decreased phagocytosis [25]. While production of oxygen radicals has been implicated in lung injury, further studies did not implicate TNF- α in smoke-induced microvascular lung injury [26]. Further evidence in other animal models suggested that that smoke inhalation, independent of burn injury, induces oxidative stress that persists for at least the first 48 hours after smoke exposure. Both lung and serum thiobarbituric acid reactive substances (TBARS) levels peaked at 24 hours after smoke exposure and remained elevated for 48 hours. In the same model, myeloperoxidase activity was also significantly elevated and increased with more severe smoke exposure [27, 28].

Other Inflammatory Mediators

Several other unique studies have investigated other markers of inflammation and injury. A study by Clark *et al.* of inhalation injury in a dog model specifically evaluated changes in lung and serum angiotensin and plasminogen. Notably, lung angiotensin converting enzyme levels decreased in the lung but remained unchanged in the serum; lung tissue plasminogen activator declined and plasma angiotensin II increased. These findings were suggestive of acute pulmonary endothelial injury [29]. Quinn *et al.* examined sulfopeptide leukotrienes and leukotriene B₄ in lung lymph and noted an increase after inhalation injury. Pre-treatment with a leukotriene B₄ antagonist prevented the expected rise in pulmonary vascular resistance [30].

TREATMENT OF INHALATION INJURY IN ANIMALS

Heparin and Xanthines

Multiple agents have been investigated to reduce and clear the protein-fibrin rich exudative casts produced during an inhalation injury [31]. Initial animal research on six sheep given intravenous heparin improved PFR, improved peak airway pressures and lowered positive end expiratory pressure (PEEP) requirements. At necropsy, the treatment group had significantly decreased amount of tracheobronchial casts. However, this benefit of improved PaO₂ was not seen

by Murakami *et al.* given combined inhalation smoke injury followed by instillation of *Pseudomonas aeruginosa* [32]. Other studies have examined the direct effect of nebulized heparin with and without the free-radical scavenger dimethylsulfoxide (DMSO) on airway sloughing [33, 34]. Brown *et al.* demonstrated improved 72-hour survival in smoke inhalation injury in sheep with nebulized heparin/DMSO group (7/7 alive) versus nebulized heparin alone (4/6 alive) versus an untreated control group (0/7 alive) [33]. Kimura *et al.* found a decrease in pulmonary vascular permeability after treatment with heparin/DMSO after smoke inhalation injury [34]. An additional study demonstrated no effect of nebulized heparin on the pulmonary shunt fraction and oxygenation requirements [35]. However, the addition of systemic lisofylline to animals treated with nebulized heparin did show improvement in pulmonary shunt fraction, as well attenuated the expected increase in arterial-alveolar gradient. This may be related to a xanthine class effect, as pentoxifylline infusion showed improved pulmonary hypertension, improved ventilation/perfusion matching and improved lung compliance compared to untreated smoke inhalation injury in sheep [36].

Nitric Oxide and Inducible Nitric Oxide Synthase

Nitric oxide (NO) has also been implicated in inflammation following smoke inhalation injury. Smoke inhalation produces cytokine release, that in turn upregulates inducible nitric oxide synthase (iNOS). This increases bronchial blood flow and decreases the hypoxic vasoconstriction reflex. This worsens ventilation-perfusion mismatch, shunt fraction, and gas exchange [37, 38]. Initially, inhaled NO was shown to attenuate hemodynamic compromises seen in inhalation injury but demonstrated only moderate improvement in decreasing hypoxia and subsequent pulmonary hypertension in two animal models [39, 40]. These effects were seen at concentrations of 20-40 parts per million with no continued improvement at higher concentrations. Based on further studies, it is now surmised that due to the nature of inhalation injuries, excessive NO may actually worsen the subsequent gas exchange abnormalities by the pathways seen above.

As such, animal studies have focused on inhibition of iNOS. Mercaptoethylguanidine (MEG) is a selective iNOS inhibitor and peroxynitrite scavenger. In sheep exposed to smoke inhalation injury and treated with MEG, there was a significant decrease in pulmonary vascular blood flow, improved PFR, decreased pulmonary vascular resistance, and decreased intrapulmonary shunt fraction [41]. These findings were also found in sheep subjected to combined 40% cutaneous burn and smoke inhalation injury [38]. More recent studies using BBS-2, a potent and highly selective iNOS inhibitor, noted similar improvements in both combined cutaneous and inhalation injuries as well as combined inhalation injury and *Pseudomonas pneumonia* [37, 42].

Other Anti-Oxidants

As another treatment related to NO, L-arginine has also been evaluated following inhalation injury. L-arginine is depleted in burn patients. With L-arginine depletion, iNOS oxidizes oxygen molecules forming superoxide radicals, which further the acute lung injury. Murakami *et al.* demonstrated that higher levels of plasma arginine concentrations due to L-arginine infusions in sheep were associated with

less of decline in PFRs and improved histopathologic scores at necropsy [43]. As previously shown, oxygen-derived free radicals and peroxynitrite produced during inhalation injury significantly add to the acute lung injury physiology. Since vitamin E (alpha-tocopherol) is an oxygen superoxide scavenger, it has been proposed as a possible therapy for inhalation injury [44]. Administration of 1000 IU vitamin E to sheep exposed to cutaneous thermal injury as well as smoke inhalation injury demonstrated improvement in pulmonary permeability index and decreased pulmonary lymph flow. This resulted in improved PFRs and peak/plateau pressure increases [45]. A similar effect was also seen in sheep subjected to the same injury but treated with nebulized alpha-tocopherol [46].

Selectin Binding

Sulfo Lewis C, a sulfated oligosaccharide, is a ligand of selectins with reported activity to bind to E-selectins. It is believed that recruitment of these adhesion molecules is part of a multi-step process of neutrophil recruitment to injured tissues. An intravenous infusion of Sulfo Lewis C after inhalation injury demonstrated attenuated lung injury compared to untreated group [47]. Attempts at blocking the adhesive interaction between neutrophils and the vascular endothelium have been also evaluated using a monoclonal antibody directed against L-selectin. These several studies have resulted in an attenuation of soft tissue permeability index, a marker of soft tissue capillary leak, in animals exposed to combined cutaneous burn and inhalation smoke injury [48, 49].

A variety of other anti-inflammatory agents and inhibitors have been investigated in single animal studies as shown in Table 1. Many of these show improvement in airway and lung injury but have not been restudied or applied to burn patient research.

TREATMENT OF INHALATION INJURY IN HUMANS

Despite the extensive research done on smoke inhalation in animal models, there is relatively little of this work that has been successfully translated to the human intensive care unit. Many of the successful therapies have been directed at mechanical pathophysiology such as airway cast formation and the reduction of barotrauma, without targeting specific inflammatory pathways. For example, albuterol is routinely used in smoke inhalation injury and intubated patients for its bronchodilatory and anti-inflammatory properties. Continuous albuterol nebulization in a sheep subjected to cutaneous thermal injury and inhalational smoke injury had improved PFRs, peak and plateau pressures and decreases shunt fraction at 48 hours compared to controls animals given saline nebulization [57]. There have been no equivalent studies in inhalation injury patients.

The use of corticosteroids to attenuate the inflammatory response in inhalation injury has been evaluated in multiple studies and had previously been used as empiric therapy for inhalation injuries. It was theorized that possible benefit might be derived from treatment with steroids in patients with isolated inhalation injury based on early rodent studies [58]. As early as 1978, Levine *et al.* demonstrated that patients with cutaneous burns and inhalation injury derived no morbidity, mortality, or pulmonary function benefit when treated with three-day courses of intravenous steroids [59]. The authors postulated that the lack of an effect may have resulted from immunosuppression leading to increased morbidity and mortality from wound and pulmonary infections. Robinson *et al.* published a retrospective, cohort study evaluating a large number of patients with isolated inhalation injury following hotel fires in Las Vegas. The study compared 141 patients who received corticosteroid therapy with 84 patients without corticosteroids, and demonstrated no

Table 1.

Author	Agent	Model	Effects of Treatment
Hales, 1995 [50]	BW-755C	Sheep	↓ lung lymph flow change, ↓ lymph protein flux, ↓ weight-to-dry lung ratio
Ikuechi, 1999 [51]	PAF antagonist	Sheep	↓ byproducts of superoxide production, both lung tissue and bronchoalveolar lavage fluid
Laffon, 1999 [52]	IL-8	Rabbit	↑ alveolar liquid clearance, ↓ extravascular water content.
Shimoda, 2003 [53]	Poly (ADP ribose) synthetase	Sheep	↓ lung edema, ↓ deterioration of gas exchange, ↓ changes in airway pressure, ↓ lung histology injury
Enkbaater, 2004 [54]	Aerosolized TPA	Sheep	↓ pulmonary airway pressures, ↓ lung water, ↑ gas exchange
Maybauer, 2006 [55]	Activated protein C	Sheep	↓ decline in PFR, ↓ pulmonary microvascular shunt fraction, ↓ peak airway pressures
Syrkina, 2007 [56]	Inhibition of JNK activation	Rodent	↑ survival time, ↓ airway apoptosis, ↓ mucous plugging, ↓ release of cytokines

detectable change in morbidity or mortality between groups [60]. Subsequent animal research in a canine model pretreated with methylprednisolone prior to smoke inhalation demonstrated no improvements in hemodynamics, gas exchange, lung compliance, lung water, pulmonary vascular permeability, or pulmonary surfactant function compared to the controls [61]. As a consequence of these studies, and because of the risks inherent in corticosteroid use in these patients, these drugs are not routinely used in patients with inhalation injury.

Bacterial pneumonia comprises a significant portion amount of morbidity and mortality beginning approximately one week after inhalation injury. The presence of secondary infection in animal models tends to aggravate pulmonary dysfunction [62]. Aerosolized antibiotics have been used in certain populations such as cystic fibrosis with good results in controlling pulmonary infections. Due to these factors, Levine *et al.* also evaluated aerosolized gentamicin following inhalation injury. This therapy demonstrated no beneficial effect on morbidity and mortality [59]. Additionally, aerosolized antibiotic treatment has been noted to be associated with the emergence of resistant strains of *Pseudomonas* and *Klebsiella*. Based on experience derived from cystic fibrosis, aerosolized colistin has recently been used as part of initial broad-spectrum treatment of pneumonia in inhalation injury patients at risk for multiple-drug resistant *Acinetobacter baumannii* infection [63].

Inhaled NO was shown to improve V/Q mismatching in inhalation injury, but only moderately improved oxygenation and decreased pulmonary arterial pressure in two animal models [39, 40]. In case series, inhaled NO improved oxygenation in some patients with severe lung failure [64]. As such, we currently provide inhaled NO to a small number of inhalation injury patients, provided an initial trial of NO effects an improvement in oxygenation. Based on further studies, it is now surmised that due to the nature of inhalation injuries, excessive NO may actually worsen the subsequent gas exchange abnormalities by the pathways seen above.

Some therapies evaluated in humans, however, have been demonstrated to be effective. Desai *et al.* demonstrated treatment modalities aimed at pathophysiologic mechanics of inhalation injury (reduction of free radicals and inhibition of fibrin cast formation) to be effective [65]. The authors evaluated 90 burn patients with concomitant inhalation injuries. Patients treated in this study with aerosolized heparin and N-acetylcysteine, showed a dramatic decrease in incidence of atelectasis, reintubation for progressive respiratory failure, number of ventilator days and overall mortality. Murakami *et al.* in 2003 reported that airway obstruction and gas exchange are not attenuated by aerosolized acetylcysteine alone, but confirmed that the combination of aerosolized acetylcysteine and heparin is effective in raising arterial blood oxygenation and in reducing other markers of lung injury [32]. Our burn center currently provides inhaled heparin to all patients with inhalation injury until extubation or bronchoscopic evidence of airway healing.

CONCLUSION

What are the future directions in the treatment of smoke inhalation injury in burn patients? There continues to be a better understanding of the pathophysiology of inhalation

injury and identification of the inflammatory mechanisms involved. Our ability to effectively treat this process is improving with advances in ventilator management. However, targeted pharmacologic therapy lacks efficacy in the relatively few human trials. The priorities for future research were well defined by Palmieri in a 2007 statement. In addition to defining a grading system for diagnosis, optimizing current treatment modalities, and improving long-term outcomes, a major recommendation was further research on the molecular mechanisms in inhalation injury and translational research for application to the burn patient with inhalation injury [66].

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